dogs) to close to zero at 12 hours, whereas in BIO–39, in humans, the urinary excretion in the first 12 hours was 1.9 mg, in the second 12 hours it was 1.7 mg; for a total of 3.06 mg for the first 24 hours. During the second 24-hour period the excretion was 2.8 mg; and this was following a single dose of medication. Regardless of whether spectrophotofluorometry is used or whether gas chromatography is used, the fact remains that the profile is very different according to these data.

As regards point #2, we note that in your submission of February 6, 1968 you state". . . This report represents a rapid and specific method for the determination of amphetamine and phentermine in human serum levels down to 2 mg/ml." In your submission of May 16, 1968 you state that ". . . it was necessary to give more than one capsule of Bionamin on the day the blood samples were collected. Only in this way would it be possible to measure blood levels with reasonable accuracy, even using this highly sensitive method." Since the serum amphetamine levels reported in BIO–46 (Dr. Austin Stough) following a dosage of 4 capsules were in the neighborhood of 50 to 100 manograms it appears that your letter of May 16, 1969 was inaccurate. Because the serum levels were determined after the four capsule doses, we are essentially examining the results of weekly dosages rather than daily dosages. High concentrations of drug are not necessarily metabolized in the same manner as low doses.

With regard to point #4 we do not believe that you have shown that lower blood levels produced by the slow absorption forms make them less susceptible to abuse, except possibly via the intravenous route. It is quite clear that abuse of these drugs taken orally will be related to the availability of the various formulations. It has been estimated that approximately 50% of all these drugs are sold illegally. Therefore it would be erroneous to conclude that differences in incidence of abuse were due solely to pharmacological differences. As Dr. Kalant[1] states: "Finally, the argument so frequently used, that scarcity of reports indicates absence of abuse has been amply demonstrated throughout this review to be unfounded."

With regard to point #7, in reply to our request for specific dates concerning study BIO–8 you merely state that you informed us "as soon as we could extract information." The reason for this request was to determine the adequacy of the monitoring of the work done for this NDA, and we are attempting to establish the manner in which these studies were assigned, performed and followed. There are serious questions regarding the following studies: 63–3–K, 65–3–L, BIO–8, BIO–13, BIO–18, BIO–42. There are contradictory summaries on BIO–44 and BIO–45; and 7 studies were cancelled without adequate explanation.

We again ask that you answer the questions listed in paragraph 7(a) of our letter of July 19, 1968.

As regards side effects, it is more a matter of safety than just minor side effects. If less danger of abuse is substantiated, this would be of greater significance than a reduction in the number of minor side effects.

ROBERT O. KNOX, M.D.,
Medical Officer.

NEW DRUG APPLICATION NO. 10–093

Test drug(s): Biphetamine (amphetamine and dextroamphetamine) Capsules Code-BIPH, (0131).

Manufacturer: Pennwalt Corp.

Studies reviewed: (3) Eugene Jolly, M.D. (Study #41093), Albert Cohen, M.D. (Study #42093); Albert Cohen, M.D. (Study #43093).

The principal objective of these studies was to demonstrate unequivocally that Biphetamine is *truly* effective rather than "possibly effective". The three clinical studies we reviewed were studies of effectiveness in producing anoraxia, i.e., weight loss in obese patients. The patients in each of these studies received treatment for 16 to 20 weeks on one of three schedules: A. Biphetamine 20 mg., given continuously. B. Biphetamine, 20 mg., given in a regimen interrupted at every fourth week by a week of placebo therapy, and C. Placebo medication given continuously. These studies were conducted in 1970 and 1971.

The tables summarize the results for this NDA. Our conclusions are based on the covarate table. For days our analysis probabilities equal to or less than 5% shall be considered to differ significantly from chance.

---

[1] Kalant, O.: The Amphetamines, Charles C. Thomas, 1966, p. 132.